1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S5

PROPRIETARY NAME AND DOSAGE FORM

STILPANE (tablets)

COMPOSITION

Each STILPANE tablet contains:

Meprobamate	150 mg
Codeine phosphate	8 mg
Paracetamol	320 mg
Caffeine anhydrous	32 mg

Excipients:

Dye lake green (C.I No's: 47005, 42090, 15985), magnesium stearate, nipastat, povidone K25, sodium starch glycollate, starch, talc.

Preservatives:

Nipastat	0,02 % *m/m*

Sugar free

CATEGORY AND CLASS

A 2.9 Other analgesics

PHARMACOLOGICAL ACTION

STILPANE tablets act as an analgesic in pain-tension states.

INDICATIONS

STILPANE is indicated for short term use (no longer than 5 days) in mild to moderate pain associated with anxiety or tension.

CONTRAINDICATIONS

STILPANE is contraindicated in:

- Hypersensitivity to any of the active ingredients or excipients of STILPANE (see COMPOSITION).
- Porphyria (including acute forms of porphyria, especially variegate porphyria, acute intermittent porphyria and hereditary coproporphyria).
- Pregnancy and lactation (see HUMAN REPRODUCTION).
- Patients with severe liver or kidney complications.
- Pulmonary insufficiency.
- STILPANE may induce convulsions in patients with a history of epilepsy.
- Obstructive airways disease, respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion.
- After operations on the biliary tract.
- Acute alcoholism.
- Head injuries and conditions in which intracranial pressure is raised.
- Comatose patients.
- During an attack of bronchial asthma or in heart failure secondary to chronic lung disease.
- Patients taking monoamine oxidase inhibitors or within fourteen days of stopping such treatment (see INTERACTIONS).

WARNINGS AND SPECIAL PRECAUTIONS

STILPANE contains paracetamol which may be fatal in overdose. In the event of overdosage or suspected overdose and notwithstanding the fact that the person may be asymptomatic, the nearest doctor, hospital or Poison Centre must be contacted immediately.

Codeine phosphate:

Exceeding the prescribed dose together with the prolonged continuous use of STILPANE may lead to dependency and addiction (see DOSAGE AND DIRECTIONS FOR USE).

Meprobamate

STILPANE should not be used for periods longer than 5 days.

Patients receiving meprobamate as contained in STILPANE should be warned that their tolerance to ingested alcohol and other depressants of the central nervous system may be lowered with consequent impairment of judgment and co-ordination.

STILPANE should be avoided in elderly and debilitated patients and in those with mental depression.

STILPANE should be used with caution in patients with impaired hepatic or renal function, and as with all sedatives, in patients with impaired respiratory functions.

Symptoms of porphyria may be exacerbated (see CONTRAINDICATIONS).

There is a serious dependence risk with a typical withdrawal syndrome.

Meprobamate may induce the hepatic microsomal enzymes involved in medicine metabolism: the metabolism of agents such as oral contraceptives, corticosteroids, phenytoin, phenothiazines, and tricyclic antidepressants may be enhanced if given concurrently (see INTERACTIONS and CONTRAINDICATIONS).

Codeine phosphate

Codeine should be given with caution to patients with hypothyroidism, adrenocortical insufficiency, asthma, impaired liver function, prostatic hypertrophy, hypotension or shock. It should be used with caution in patients with inflammatory or obstructive bowel disorders, and myasthenia gravis.

Administration of STILPANE during labour may cause respiratory depression in the new-born infant.

The depressant effects of codeine are enhanced by depressants of the central nervous system such as alcohol, anaesthetics, hypnotics and sedatives, and phenothiazines (see INTERACTIONS).

The prolonged use of high doses of codeine has produced dependence of the morphine type.

Depending on the genetic variability of CYP2D6, the individual metabolizing capacity for codeine may vary. Even therapeutic doses can lead to increased formation of the active metabolite morphine resulting in clinical signs of morphine intoxication (see KNOWN SYMPTOMS OF OVERDOSAGE and SIDE EFFECTS of Codeine).

Paracetamol

Paracetamol dosages in excess of those recommended may cause severe liver damage. Prolonged excessive use can cause irreversible kidney damage.

Dosages in excess of those recommended may cause severe liver damage. Patients suffering from liver or kidney disease should take STILPANE under medical supervision. Consult your doctor if no relief is obtained from the recommended dosage. STILPANE should be given with care to patients taking other medicines that affect the liver, e.g. barbiturates (see KNOWN SYMPTOMS OF OVERDOSAGE).

Caffeine

Caffeine should be given with caution to patients with peptic ulceration, hyperthyroidism, hypertension, epilepsy, cardiac dysrhythmias, or other cardiovascular disease as these conditions may be exacerbated. Caffeine should also be given with caution to patients with heart failure, hepatic dysfunction, chronic alcoholism, acute febrile illness, neonates and elderly, since in all of these circumstances the clearance may be decreased resulting in increases in serum concentrations of caffeine and serum half-life.

Severe overdosage or idiosyncrasy due to caffeine may lead to agitation, diuresis, repeated vomiting with extreme thirst, delirium, hyperthermia, cardiac dysrhythmias including tachycardia, electrolyte disturbances, convulsions and death.

Effects on ability to drive and use machines

The use of STILPANE may lead to drowsiness and impaired concentration that may be aggravated by the simultaneous intake of alcohol or central nervous system depressants.

Affected patients should not drive or operate machinery (see SIDE EFFECTS).

INTERACTIONS

Caffeine

Caffeine undergoes extensive metabolism by hepatic microsomal cytochrome P450 isoenzyme CYP1A2, and is subject to interactions with other medicines which enhance or reduce its metabolic clearance.

Alcohol: Caffeine and alcohol causes a synergistic interaction which further increases reaction time.

Antidysrhythmics: Mexiletine reduces the elimination of caffeine.
Lidocaine, flecainide and tocainide have no effect on caffeine elimination.

Antibacterials: Caffeine elimination half-life increases and the clearance decreases when given with ciprofloxacin, enoxacin and pipemidic acid, whereas lomefloxacin, norfloxacin and ofloxacin have little or no effect on these parameters.

Antidepressants: Fluvoxamine reduces the clearance and prolongs the elimination half-life of caffeine.

Antiepileptics: The mean clearance of caffeine increases and its half-life decreases in epileptic patients taking phenytoin. Treatment with carbamazepine or valproic acid have no effect.

Gastrointestinal medicines: Cimetidine reduces the systemic clearance of caffeine and prolongs its elimination half-life.

Lithium: Lithium concentrations increase when caffeine is eliminated from the diet. Toxicity may occur in patients maintained at higher concentrations.

Methoxsalen: Methoxsalen reduces the clearance of caffeine in patients with psoriasis.

Sex hormones: Oral contraceptives reduce the clearance and increases the elimination half-life of caffeine.

Sympathomimetics: The use of caffeine with phenylpropanolamine produces greater plasma-caffeine concentrations, greater increases in blood pressure and more reports of physical adverse effects than either medicine alone. Giving caffeine with ephedrine produce cardiovascular, metabolic and hormonal responses, increased systolic blood pressure and heart rate, as well as raised fasting glucose and insulin.

Meprobamate

The sedative effects of meprobamate are enhanced by CNS depressants including alcohol. Meprobamate is capable of inducing hepatic microsomal enzyme systems involved in medicine metabolism: the metabolism of other medicines may be enhanced if given concurrently.

Paracetamol

Paracetamol toxicity may be increased in patients receiving other potentially hepatotoxic medicines or medicines that induce liver microsomal enzymes. The absorption of paracetamol may be accelerated by medicines such as metoclopramide. Excretion may be affected and plasma concentrations altered when given with probenecid. Cholestyramine reduces the absorption of paracetamol if given within 1 hour of paracetamol.

Antibacterials: Severe hepatotoxicity at therapeutic doses or moderate overdose of paracetamol has been reported in patients receiving isoniazid, alone or with other medicines for tuberculosis.

Anticoagulants: STILPANE has no effect on the gastric mucosa or on platelet function, caution should be observed, since an increased risk of bleeding in patients taking regular doses of paracetamol while on an oral anticoagulant have been observed. An increase in INR has also been reported, therefore increased monitoring may be appropriate.

Antiepileptics: Enzyme inducing medicines such as carbamazepine, phenobarbital, phenytoin or primidone increases paracetamol metabolism (glucuronidation and oxidation) and clearance from the body. This could result in an increased production of the hepatotoxic metabolite of paracetamol. If this toxic metabolite then exceeds the normal glutathione binding capacity, liver damage may occur. Therefore, the plasma-paracetamol concentrations should be halved in patients receiving enzyme-inducing medicines. Paracetamol reduces the area under the plasma concentration-time curve for lamotrigine, and its half-life, and increased the percentage of lamotrigine recovered in the urine.

Antivirals: Paracetamol enhances the antiviral effect of Inteferon Alfa. Severe hepatotoxicity has occurred after the use of paracetamol in patients taking zidovudine and co-trimoxazole.

Probenecid: Pretreatment with probenecid can decrease paracetamol clearance and increase its plasma half-life.

Codeine phosphate

The depressant effects may be exaggerated and prolonged by phenothiazines, monoamine

oxidase (MAO) inhibitors, and tricyclic antidepressants (see CONTRAINDICATIONS).

Codeine also increases the degree of sedation and the hypotensive effects of phenothiazines. Phenothiazines seem to be antianalgesic and increases the amount of opioid required to produce satisfactory relief from pain.

A number of antihistamines e.g. hydroxyzine enhance the analgesic effects of low doses of opioids.

HUMAN REPRODUCTION

The safety of STILPANE in pregnancy and lactation has not been established.

STILPANE should not be used during pregnancy and lactation (see CONTRAINDICATIONS).

DOSAGE AND DIRECTIONS FOR USE

For short term use only. Do not use STILPANE for longer than 5 days.

Not recommended for children under 12 years of age.

Take two tablets three or four times a day as required.

DO NOT EXCEED THE RECOMMENDED DOSE.

SIDE EFFECTS

Paracetamol

Blood and the lymphatic system disorders

Frequency unknown: Neutropenia, pancytopenia, leucopenia, thrombocytopenia and agranulocytosis

Skin and subcutaneous tissue disorders

Less frequent: Sensitivity reactions resulting in reversible skin rash, usually erythematous or urticarial

Frequency unknown: Sensitivity reactions accompanied by medicine fever and mucosal lesions

Codeine phosphate

Nervous system disorders

Frequent: Drowsiness

Less frequent: Confusion, euphoria, mood changes, restlessness, miosis, hallucinations, sedation, dizziness, faintness. Large doses of codeine can cause excitement and convulsions

Frequency unknown: Deepening coma, vertigo, hypothermia, raised intracranial pressure

Cardiac disorders

Less frequent: Bradycardia, palpitations, orthostatic hypotension, facial flushing

Gastrointestinal disorders

Frequent: Constipation

Less frequent: Dry mouth, nausea, vomiting

Skin and subcutaneous tissue disorders

Less frequent: Pruritus, urticaria, sweating

Frequency unknown: Contact dermatitis, itching of the nose and idiosyncrasy

Musculoskeletal, connective tissue and bone disorders

Less frequent: Muscle rigidity following high doses

Renal and urinary disorders

Less frequent: Difficulty in micturition

Caffeine anhydrous

Nervous system disorders

Frequent: Insomnia, headache, anxiety, restlessness

Frequency unknown: Vertigo, palpitations, tremor and hypotension

Gastrointestinal disorders

Frequent: Nausea, vomiting, abdominal pain

Less frequent: Gastrointestinal bleeding

Meprobamate

Blood and the lymphatic system disorders

Frequency unknown: Agranulocytosis, eosinophilia, leucopenia, thrombocytopenia, and aplastic anaemia

Nervous system disorders

Frequent: Drowsiness, ataxia

Less frequent: Weakness, headache, disturbances of vision, excitement, dizziness

Frequency unknown: Paraesthesia

Cardiac disorders

Less frequent: Tachycardia and cardiac dysrhythmias

Frequency unknown: Hypotension

Gastrointestinal disorders

Less frequent: Nausea, vomiting, diarrhoea

Skin and subcutaneous tissue disorders

Less frequent: Skin rashes, urticaria

Frequency unknown: Purpura, angio oedema, bronchospasm, anuria, erythema multiforme

Treatment should be discontinued as soon as these hypersensitivity reactions occur.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Prompt treatment is essential. In the event of overdosage, consult a doctor immediately, or take the patient to the nearest hospital immediately. A delay in starting treatment may mean that antidote is given too late to be effective. Evidence of liver damage is often delayed until after the time for effective treatment has lapsed.

Susceptibility to paracetamol toxicity is increased in patients who have taken repeated high doses (greater than 5 to 10 g/day) of paracetamol for several days, in chronic alcoholism, chronic liver disease, AIDS, malnutrition, and with the use of medicines that induce liver microsomal oxidation such as barbiturates, isoniazid, rifampicin, phenytoin and carbamazepine.

Symptoms of paracetamol overdosage in the first 24 hours are pallor, nausea, vomiting, anorexia and possibly abdominal pain.

Liver damage may become apparent 12 to 48 hours after ingestion. Abnormalities of glucose metabolism and metabolic acidosis may occur. Acute renal failure with acute tubular necrosis

may develop even in the absence of liver damage.

Cardiac dysrhythmias have been reported.

Symptoms during the first two days of acute poisoning do not reflect the potential seriousness of the overdosage. Liver damage may manifest initially by elevation of the serum transaminase and lactic dehydrogenase activity, increased serum bilirubin concentration and prolongation of the prothrombin time. Liver damage may progress to encephalopathy, coma and death. Central oedema and non-specific myocardial depression have also occurred.

Treatment of paracetamol overdosage:

Although evidence is limited it is recommended that any adult person who has ingested 5 to 10 grams or more of paracetamol (or a child who has had more than 140 mg/kg) within the preceding 4 hours, should undergo gastric lavage (emesis may be adequate for children) and a single dose of 50 g activated charcoal given via the lavage tube. Ingestion of amounts of paracetamol smaller than this may require treatment in patients susceptible to paracetamol poisoning (see above). In patients who are stuperose or comatose, endotracheal intubations should precede gastric lavage in order to avoid aspiration.

N-acetylcysteine should be administered to all cases of suspected overdose as soon as possible, preferably within eight hours of overdosage, although treatment up to 36 hours after ingestion may still be of benefit, especially if more than 150 mg/kg of paracetamol was taken.

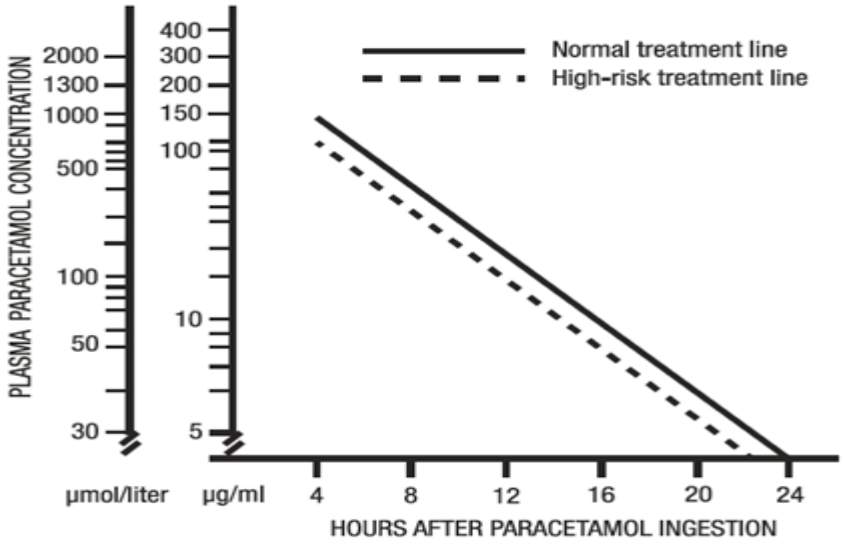
IV: An initial dose of 150 mg/kg in 200 ml glucose injection, given **intravenously** over 15 minutes, followed by an infusion of 50 mg/kg in 500 ml glucose injection over the next 4 hours, and then 100 mg/kg in 1 000 ml dextrose injection over the next 16 hours.

The volume of intravenous fluid should be modified for children.

Orally: Although the oral formulation is not the treatment of choice, 140 mg/kg dissolved in water as a 5 % solution may be administered initially, followed by 70 mg/kg every 4 hours for 17 doses. Acetylcysteine is effective if administered preferably within 8 hours of overdosage.

If N-acetylcysteine is not available, methionine 2,5 mg may be given immediately, followed by 2,5 g every 4 hours for 3 doses. Patients should however, preferably be transferred to a facility where N-acetylcysteine can be given.

A plasma paracetamol level should be determined 4 hours after ingestion in all cases of suspected overdosage. Levels done before 4 hours, unless high may be misleading. Patients at risk of liver damage, and hence requiring continued treatment with N-acetylcysteine, can be identified according to their plasma paracetamol level. The plasma paracetamol level can be plotted against time since ingestion in the nomogram below.



Those, whose plasma paracetamol levels are above the “normal treatment line”, should

continue N-acetylcysteine treatment with 100 mg/kg IV over 16 hours repeatedly until recovery. Patients with increased susceptibility to liver damage as identified above, should continue treatment if concentrations are above the “high-risk treatment line”. INR correlates best with survival. All patients with significant ingestions should be monitored for at least 96 hours.

Other symptoms include central stimulation and exhilaration, followed by cardiovascular collapse and coma.

Overdosage with barbiturates can cause severe or even fatal hypotension, respiratory depression, shock, heart failure and ultimately death (see WARNINGS AND SPECIAL PRECAUTIONS of Paracetamol).

Patients should be managed with intensive symptomatic and supportive therapy with particular attention being made to the maintenance of cardiovascular, respiratory, renal function and to the maintenance of electrolyte balance.

IDENTIFICATION

Green, biconvex tablet, debossed “C26” on the one side and bisected on the other side.

PRESENTATION

100 tablets are packed in aluminium/PVC blister strips. The strips are packed, together with a leaflet into a unit carton.

500 tablets are packed into a white polypropylene (PP) securitainer, together with a foam insert and a leaflet and sealed with a white polyethylene cap.

1 000 tablets are packed into amber PVC jars together with a foam insert and a leaflet and sealed with a screwcap.

Not all packs and pack sizes are necessarily marketed.

STORAGE INSTRUCTIONS

Store at or below 25 °C, in a well-closed container.

Protect from light.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

M/2.9/2

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

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DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

Date of registration: 23 November 1979

Date of the most recent amendment to the professional information as approved by the Authority: 20 April 2012

Botswana: B9322890 1C

Namibia: NS3 10/2.9/0565

ZA_STILTAB_1204_03